An Approach to 2,3-Methanoamino Acids with Extended Side Chains: Syntheses of *trans*-BOC-cyclo-Lys(CBZ)-OH, *trans*-BOC-cyclo-Glu-OEt, and *trans*-BOC-cyclo-Arg(CBZ)-OH

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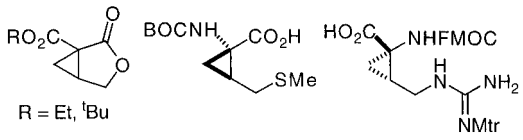
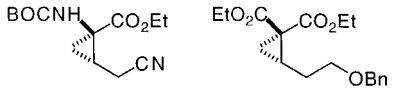
Lactone **1**, available as either antipode from D-mannitol or L-gulono-1,4-lactone,[1,2] is a valuable starting material for syntheses of methanoamino acids[3] with 3-substituents that are functionalized methylene groups (CH_2X, X = heteroatom).[4] For instance, it has been used to prepare the 2,3-methanoamino acids **2**[5] and **3**[6] efficiently. Chiron **1** also has been used in syntheses of 2,3-methanoamino acids with functionalized ethylene substituents (CH_2-CH_2X, X = heteroatom).[7] These reaction sequences involved S_N2-displacements with cyanide as a nucleophile to obtain intermediates such as **4**. Unfortunately, these displacements add steps to the route, and they are not particularly efficient reactions since the leaving group is proximal to the cyclopropane ring. Moreover, hydrolysis of the nitrile functionality in **4** was not straightforward, and attempts to circumvent this by using nucleophiles other than cyanide were unsuccessful.



1 **2** **3**

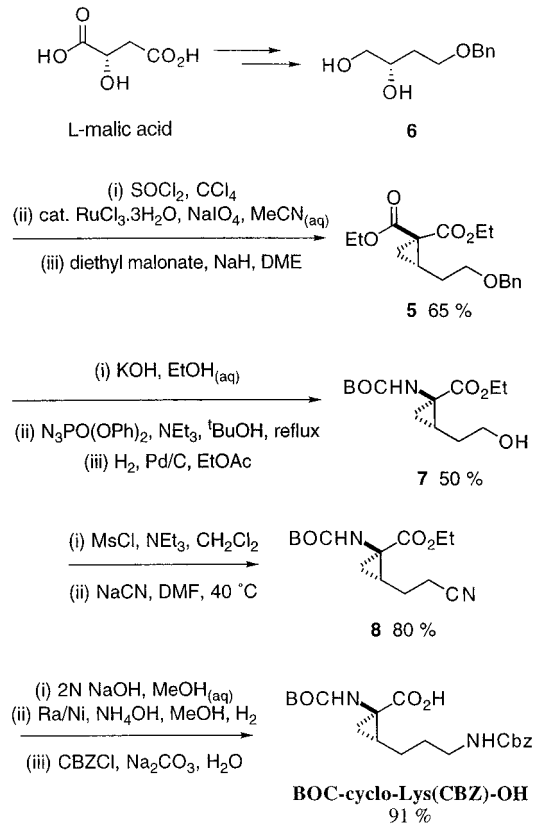


4 **5**

This paper reports a synthesis of the cyclopropane chiron **5** from L-malic acid and reaction sequences that demonstrate that this chiron is well-suited to syntheses of the hitherto less accessible cyclopropyl analogues of amino acids. Specifically, this starting material is useful for the preparation of 2,3-methanoamino acids with extended side chains. Three products made to prove this assertion were *trans*-BOC-cyclo-Lys(CBZ)-OH, *trans*-BOC-cyclo-Glu-OEt, and *trans*-BOC-cyclo-Arg(CBZ)-OH.

The optically pure diol **6** was conveniently obtained on a 50 g scale via published procedures that do not involve chromatography (Scheme 1).[8] Diol **6** was reacted with

Scheme 1. Synthesis of *trans*-BOC-cyclo-Lys(CBZ)-OH



thionyl chloride to give a cyclic sulfite,[9] oxidized via Sharpless conditions,[10] and then reacted with diethyl malonate to give chiron **5**.[11] None of the intermediates in these three steps was purified. Selective hydrolysis of the less hindered ester, Curtius rearrangement, and hydrogenolysis gave the BOC-protected amino alcohol **7**. Mesylation of **7** and displacement with cyanide gave the nitrile **8** in good yield. Hydrolysis of the ester functionality in **8**, catalytic reduction of the nitrile group, and protection with a carboxybenzyl group gave the first product in this series in a protected form suitable for solid-phase syntheses, *i.e.*, *trans*-BOC-cyclo-Lys(CBZ)-OH. As far as we are aware, this is the first reported synthesis of any optically pure 2,3-methanolysine derivative, although other interesting constrained Lys analogues have been reported.[12]

Intermediates in the synthesis of BOC-cyclo-Lys(CBZ)-OH were then used to prepare other 2,3-methanoamino acid derivatives. A Sharpless oxidation of **7** at the hydroxyethyl functionality converted it to BOC-cyclo-Glu-OEt; overall, this route is much more efficient than the one we originally developed for this same product.[7] Similarly, a Mitsunobu reaction of alcohol **7** with a guanidine nucleophile[13] gave *trans*-BOC-cyclo-Arg(CBZ)-OH after hydrolysis (Scheme 2). The yield of this product was diminished due to cleavage of one of the guanidine-

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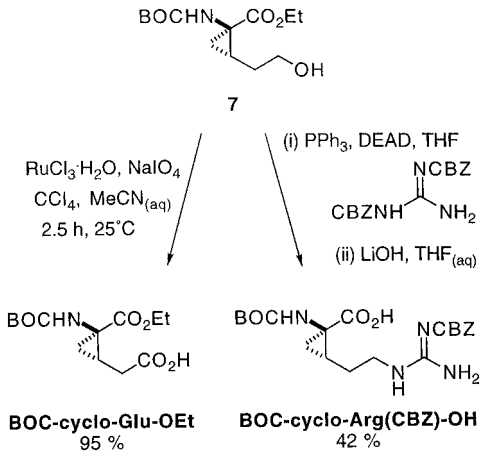
Scheme 2. Synthesis of *trans*-BOC-cyclo-Glu-OEt and *trans*-BOC-cyclo-Arg(CBZ)-OH



CBZ protecting groups in competition with ester hydrolysis. This is, however, a relatively minor problem that will be solved when these syntheses are optimized.

Experimental Section

General Procedures. Melting points were uncorrected. Proton NMR spectra were recorded at 200 or 300 MHz and ^{13}C spectra at 50 or 75.4 (δ ppm). Where necessary, the carbon multiplicities were determined via APT experiments. Thin-layer chromatography was performed on silica gel 60 F_{254} plates. Flash chromatography was performed on silica gel (230−600 mesh). DMF was stored over 4 Å molecular sieves for 1 week before use, and CH_2Cl_2 and *t*-BuOH were distilled from appropriate drying agents. Other chemicals were purchased from commercial suppliers and used as received.

(*S*)-Diethyl 2-[(Benzyloxy)ethyl]cyclopropane-1,1-dicarboxylate (5). Thionyl chloride (10.9 mL, 150 mmol) was added to the solution of the benzyl protected diol **6** (24.5 g, 125 mmol) in CCl_4 (100 mL), and the mixture was heated to reflux for 1 h. The reaction mixture was cooled to 0 °C and diluted with 100 mL of CH_3CN. Sodium periodate (40.1 g, 188 mmol) and $RuCl_3 \cdot 3H_2O$ (ca. 20 mg) were added to the above solution, followed by H_2O (150 mL). The resulting orange mixture was stirred vigorously for 2 h at 25 °C and then extracted with ether (300 mL). The organic layer was washed with water, saturated $NaHCO_3$ solution, and brine and then dried over Na_2SO_4. After filtration through a pad of silica gel, the organic layer was concentrated to yield 26.3 g of the crude cyclic sulfate. This cyclic sulfate was slowly added to a solution of sodium diethyl malonate prepared by addition of sodium hydride (5.18 g, 95%, 214 mmol) to the solution of diethyl malonate (15.5 mL, 102 mmol) in 500 mL of dimethoxyethane. The reaction mixture was heated to reflux for 20 h and then cooled to 25 °C. After evaporation of the organic solvent, the residue was extracted with EtOAc (200 mL × 2), and the extract was washed with saturated $NaHCO_3$ solution, H_2O, and brine and then dried over Na_2SO_4. After evaporation of the solvent, 26 g of the crude product **5** was obtained as an oil and used in the next step without further purification. A relatively pure sample of **5** was obtained via column chromatography (50% Et_2O/*n*-C_6H_{14}) for characterization purposes: R_f 0.57 (67% ether/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.15 (m, 5H), 4.50 (s, 2H), 4.25−4.05 (m, 4H), 3.54 (t, J = 6.6 Hz, 2H), 2.10−1.95 (m, 1H), 1.85−1.70 (m, 1H), 1.6−1.45 (m, 1H), 1.42−1.35 (m, 2H), 1.30−1.20 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.1, 168.0, 138.3, 128.7, 128.2, 127.4, 72.8, 69.0, 61.23, 61.18, 29.0, 25.1, 20.5, 14.0, 13.9; IR ($CDCl_3$) 2982, 2938, 2863, 1728, 1369, 1320 cm^{-1}; $[\alpha]^{25}_D$ −0.6° (c = 1.45, CH_2Cl_2); HRMS (FAB/DP) m/z calcd for $C_{18}H_{24}O_5$ 343.1522, found 343.1519 for $[M + Na]^+$.

(1*R*,2*S*)-Ethyl 1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-(hydroxyethyl)cyclopropane-1-carboxylate (7). The crude diethyl dicarboxylate derivative **6** (18.0 g, 61.6 mmol) was dissolved in 67.8 mL of EtOH. An aqueous KOH solution (1 M, 67.8 mL, 1.1 equiv) was added at 0 °C, and then the solution was allowed to warm to 25 °C and stirred for 16 h. The reaction mixture was concentrated and extracted with ether (200 mL × 3). The aqueous layer was acidified with concd HCl and extracted with ether (300 mL × 2), and then the organic layer was washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent, 10.2 g of the crude product was obtained and used for the next step without purification (63% yield). A small sample was purified via column chromatography for further characterization: R_f 0.56 (60% EtOAc/hexane with trace AcOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 5H), 4.50 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 4.6−4.45 (m, 2H), 2.25−2.15 (m, 1H), 1.97−1.85 (br, 2H), 1.75−1.67 (br, 1H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.6, 137.9, 128.7, 128.4, 127.7, 126.8, 73.1, 69.0, 62.5, 34.2, 28.4, 23.8, 14.0; IR (neat) 2982, 1735, 1453, 1375, 1320, 1206, 1147 cm^{-1}; $[\alpha]^{25}_D$ +2.6° (c = 1.7, CH_2Cl_2); +FAB/DP m/z calcd for $C_{16}H_{20}O_5$; 292 found 315 for $[M + Na]^+$.

The crude monocarboxylic acid derivative prepared above (10.0 g, 37.9 mmol) and NEt_3 (8.12 mL, 37.7 mmol) were mixed with dry *t*-BuOH (100 mL) at 25 °C under N_2. Diphenyl phosphorazidate (4.16 g, 42.0 mmol) was added, and the reaction mixture was refluxed with stirring for 12 h. The reaction solution was concentrated, and the crude product was extracted with ether. After being washed with 1 N HCl and saturated $NaHCO_3$(aq) and dried, 11.2 g of the crude product was obtained (81% yield). A relatively pure sample was obtained via column chromatography (33% Et_2O/*n*-C_6H_{14}) for characterization purposes: R_f 0.53 (50% ether/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 5H), 4.47 (s, 2H), 4.2−4.0 (m, 2H), 3.55−3.4 (m, 2H), 1.95−1.8 (m, 2H), 1.65−1.5 (m, 2H), 1.43 (s, 4H), 1.21 (t, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.4, 155.8, 138.4, 128.2, 127.5, 79.6, 72.7, 69.1, 61.0, 28.7, 27.1, 22.5, 14.1; $[\alpha]^{25}_D$ +0.8° (c = 1.55, CH_2Cl_2); +FAB/DP m/z calcd for $C_{20}H_{29}NO_5$ 363, found 386 for $[M + Na]^+$.

A mixture of the BOC-protected ester formed as described above (11.2 g, 30.8 mmol) and 10% Pd/C (1.0 g) in MeOH (100 mL) was stirred for 12 h at 25 °C under a hydrogen balloon. The reaction solution was filtered through a silica gel pad and washed with MeOH (ca. 200 mL). The filtrate was evaporated to give 8.05 g of the crude product **7** (96% yield). A pure sample was obtained via column chromatography (50% Et_2O/*n*-C_6H_{14}) for characterization purposes: R_f 0.46 (67% ether/hexane); ^1H NMR (200 MHz, $CDCl_3$) δ 5.42 (bs, 1H), 4.2−3.97 (m, 2H), 3.74−3.45 (m, 2H), 1.98−1.8 (m, 1H), 1.80−1.45 (m, 2H), 1.38 (s, 9H), 1.4−1.28 (m, 1H), 1.18 (t, J = 7.1 Hz, 1H), 1.2−1.06 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.5, 157.3, 80.3, 61.6, 61.3, 37.6, 30.3, 29.4, 28.2, 21.3, 14.1; IR ($CDCl_3$) 3360, 2980, 1698, 1506, 1393, 1369, 1280, 1185 cm^{-1}; $[\alpha]^{25}_D$ +3.4° (c = 1.5, CH_2Cl_2); HRMS (+FAB/DP) m/z calcd for $C_{13}H_{23}NO_5$ 296.1474, found 296.1493 for $[M + Na]^+$.

(1*R*,2*R*)-Ethyl 1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-(cyanoethyl)cyclopropane-1-carboxylate (8). A solution of the hydroxyethyl derivative **7** (1.6 g, 5.86 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C, NEt_3 (0.548 mL, 7.03 mmol, 1.2 equiv) and then methanesulfonyl chloride (0.978 mL, 7.03 mmol) were added, and the solution was stirred for 5 h at 25 °C under N_2. The reaction solution was concentrated, and the residue was extracted with ether. After being washed with water and brine, the organic layer was concentrated to yield the crude mesylate.

The crude mesylate formed above was treated with KCN (954 mg, 14.7 mmol) and 18-crown-6 (310 mg, 1.17 mmol) in DMF (20 mL) and then stirred for 4 h at 70 °C and for 12 h at 40 °C. The reaction solution was concentrated and extracted with ether (100 mL). The organic layer was washed with water, saturated $NaHCO_3$, and brine and then concentrated to give a 1.66 g of the crude nitrile. The crude material (1.31 g) was partially purified via silica gel column chromatography (Et_2O/Hex, 1:1) to yield 1.05 g of the product **8** as an oil (80% yield). A pure sample was obtained via column chromatography (50% Et_2O/*n*-C_6H_{14}) for characterization purposes: R_f 0.32 (50% ether/hexane); ^1H NMR (200 MHz, $CDCl_3$) δ 5.13 (br, 1H), 4.25−4.13 (m, 2H), 2.5−2.37 (brt, J = 6.8 Hz, 2H), 2.1−1.9 (brq, J = 7 Hz, 2H), 1.67−1.56 (m, 1H), 1.54−1.46 (m, 1H), 1.44 (s, 9H), 1.4−1.32 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.4, 155.8, 119.4, 80.1, 61.6, 38.2, 30.4, 28.3, 23.0, 22.9, 16.9, 14.2; IR (neat) 3362, 2979, 2247, 1718, 1701, 1507, 1369, 1251,

1184 cm^{-1}; $[\alpha]^{25}_D$ −0.1° (*c* = 1.35, CH_2Cl_2); HRMS (+FAB/DP) *m/z* calcd for $C_{14}H_{22}N_2O_4$ 305.1477, found 305.1494 for $[M + Na]^+$.

(1*R*,2*R*)-2-[[[(Benzyloxycarbonyl)]amino]ethyl]-1-[*N*-(*tert*-butoxycarbonyl)amino]cyclopropane-1-carboxylic Acid. A solution of the nitrile ester **8** (585 mg, 2.06 mmol) in MeOH (3 mL) was cooled to 0 °C, and a 2 N NaOH solution (3.6 mL, 7.21 mmol, 3.5 equiv) was added with stirring. After 10 h of stirring at 25 °C, the reaction mixture was concentrated to remove the organic solvent and washed with ether (20 mL × 2) to remove nonacidic byproducts. The aqueous solution was acidified with 2 N HCl and then extracted with ether (20 mL × 2) and EtOAc (20 mL × 2). After evaporation of the solvent, 522 mg of the crude acid was obtained (99% yield). A pure sample was obtained via column chromatography (50% Et_2O/*n*-C_6H_{14}) for characterization purposes: R_f 0.38 (60% ether/hexane with trace AcOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (bs, 1H), 2.57−2.44 (bm, 2H), 2.13−2.02 (bm, 2H), 1.78−1.64 (m, 1H), 1.62−1.54 (m, 1H), 1.54−1.4 (overlapping, 1H), 1.44 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.9, 156.1, 119.4, 80.5, 37.8, 31.2, 28.2, 23.6, 23.1, 16.7; IR ($CDCl_3$) 2979, 2252, 1707, 1507, 1393, 1368, 1164 cm^{-1}; $[\alpha]^{25}_D$ −0.1° (*c*=1.6, CH_2Cl_2).

A mixture of the cyano acid derivative (138 mg, 0.543 mmol), NH_4OH (0.367 mL, 5.43 mmol), and a catalytic amount of Raney-Ni in MeOH (6 mL) was stirred for 6 h in a Parr reactor under H_2 (300 psi). The reaction solution was filtered through a cotton plug and washed with MeOH/H_2O. After evaporation of the solvent, the crude amino acid was obtained (136 mg): ^{1}H NMR (300 MHz, D_2O) δ 2.87 (bs, 2H), 1.58 (br, 2H), 1.29 (s, 9H), 1.5−1.15 (overlapping, 4H), 0.95 (br, 1H); ^{13}C NMR (75.4 MHz, D_2O) δ 166.7, 161, 89.6, 55.9, 47.8, 36.3, 35.1, 32.7, 29.8. This material was used for the next step without purification.

The crude amino acid (96 mg, 0.372 mmol) was dissolved in 50% concentrated Na_2CO_3 (1 mL), stirred for 10 min at 25 °C, and then cooled to 0 °C. Carbobenzyloxy chloride (64 μL, 1.2 equiv) was added dropwise with vigorous stirring, and then the mixture was stirred for 2 h at 0 °C. The reaction solution was acidified with 2 M HCl and extracted with EtOAc. The organic layer was washed with water and brine and then dried over $MgSO_4$. After evaporation of the solvent, 138 mg of *trans*-BOC-cyclo-Lys(CBZ)-OH was obtained. A pure sample was obtained via column chromatography (50% Et_2O/*n*-C_6H_{14}) for characterization purposes: R_f 0.47 (60% ether/hexane with trace AcOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.41−7.22 (m, 5H), 5.05 (s, 2H), 3.2−3.05 (bs, 2H), 1.7−1.5 (bs, 4H), 1.5−1.3 (br, 2H), 1.42 (s, 9H), 1.2−1.1 (br, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.3, 156.6, 152.2, 136.6, 128.5, 128.1, 80.5, 66.6, 40.1, 32.0, 29.2, 28.3, 24.5, 23.6; IR (neat) 3337, 2975, 2929, 1701, 1522, 1368, 1255, 1165 cm^{-1}; $[\alpha]^{25}_D$ +0.7° (*c* = 1.3, CH_2Cl_2); HRMS(+FAB/DP) *m/z* calcd for $C_{20}H_{28}N_2O_6$ 393.2025, found 393.2040 for $[M + H]^+$.

(1*R*,2*S*)-Ethyl 1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-(carboxymethyl)cyclopropane-1-carboxylate. The alcohol **7** (0.10 g, 0.366 mmol) was dissolved in 3.5 mL of CCl_4−CH_3CN−H_2O (2:2:3). Sodium periodate (235 mg, 1.10 mmol) was added, followed by $RuCl_3 \cdot H_2O$ (3 mg). The reaction mixture was stirred for 2.5 h at 25 °C and then extracted with EtOAc (10 mL × 2). The combined organic layers were passed through a pad of silica gel and concentrated to yield 100 mg of *trans*-BOC-cyclo-Glu-OEt (95% yield): R_f 0.45 (60% EtOAc/hexane with trace AcOH); mp 115−115.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.26 (br s, 1H), 5.46 (br s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.92−2.55 (br m, 2H), 1.81−1.63 (m, 1H), 1.58−1.25 (overlapping, 2H), 1.43 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.6, 171.7, 157.2, 81.2, 62.1, 38.7, 32.9, 28.7, 26.4, 23.2, 14.6; IR ($CHBr_3$) 1707, 1490, 1392, 1369, 1324, 1247 cm^{-1}; +FAB/DP *m/z* calcd for $C_{13}H_{21}NO_6$ 287, found 288 for $[M + H]^+$; $[\alpha]^{20}_D$ +6.0° (*c* = 1.14, CH_2Cl_2). Anal. Calcd for $C_{13}H_{21}N_1O_6$: C, 54.34; H, 7.37; N, 4.88 Found: C, 53.84; H, 7.24; N, 4.83.

(1*R*,2*R*)-2-[[(Benzyloxycarbonyl)guanidinyl]ethyl]-1-[*N*-(*tert*-butoxycarbonyl)amino]cyclopropane-1-carboxylic Acid. Triphenylphosphine (1.24 g, 4.71 mmol, 1.25 equiv) and bis(benzyloxycarbonyl)guanidine (1.70 g, 5.20 mmol, 1.38 equiv) were added to a solution of the hydroxyethyl derivative **7** (1.03 g, 3.77 mmol) in THF (50 mL) under N_2. This solution was cooled to 0 °C, diethyl azodicarboxylate (0.742 mL, 4.71 mmol, 1.25 equiv) was slowly added over 30 min, and the reaction mixture was then stirred for 20 h at 25 °C under N_2. The reaction solution was concentrated, and the residue was extracted with EtOAc. The organic layer was washed with water and brine and then concentrated to yield 3.0 g of the crude protected guanidine product with two CBZ groups, *i.e.*, *trans*-BOC-cyclo-Arg(CBZ)$_2$-OH: +FAB/DP *m/z* calcd for $C_{30}H_{38}N_4O_8$ 582, found 583 for $[M + H]^+$.

A sample of the material synthesized above (2.32 g) was dissolved in THF (30 mL) and reacted with 1 M LiOH (20 mL) for 10 d at 25 °C. A white solid formed and was removed by filtration, and the filtrate was extracted with ether (20 mL × 3). The aqueous layer was acidified with 2 M HCl and extracted with a 1:1 EtOAc−ether mixture (40 mL). The organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated to yield 520 mg of *trans*-BOC-cyclo-Arg(CBZ)-OH as an amorphous solid (42% yield overall from **7**): mp 125−140 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.47−7.20 (m, 5H), 6.30 (br s, 1H), 5.15 (br s, 2H), 3.58−3.30 (br, 2H), 2.18−1.85 (br, 2H), 1.40−1.22 (overlapping, 2H), 1.34 (s, 9H), 1.04−1.14 (br s, 1H); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 174.0, 151.8, 151.2, 150.9, 131.5, 123.9, 123.4, 123.3, 73.2, 62.5, 36.9, 33.9, 23.5, 22.3, 21.9, 16.8; IR ($CHBr_3$) 1718, 1612, 1497, 1400, 1366 cm^{-1}; HRMS (+FAB/DP) *m/z* calcd for $C_{20}H_{28}N_4O_6$ 421.2087, found 421.2085 for $[M + H]^+$.

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